REMARKS

Examination of claims 39, 43, 44, and 46-57, and the species of cationic lipids, is reported in the present Office Action. Claims 39, 50, 51, and 57 were rejected under the judicially-created Doctrine of Obviousness-Type Double Patenting; claims 39 and 46-38 were rejected under 35 U.S.C. § 112, second paragraph; claims 39, 44, and 49-57 were rejected under 35 U.S.C. § 102(e); and claims 39 and 43 were rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed as follows.

First, applicants note that the phrase "Brief Description of the Drawings" was inserted into the specification on page 24, just before the pre-existing description of the drawings. Also, the Abstract on page 49 of the application has been identified as the "Abstract of the Disclosure."

Double Patenting Rejection

Claims 39, 50, 51, and 57 were rejected under the judicially-created Doctrine of Obviousness-Type Double Patenting over claims 1, 9-11, and 26 of U.S. Patent No. 6,126,938. This rejection is respectfully traversed.

The rejection is based on the Examiner's assertion that the cited claims of the present application are generic in relation to the cited claims of the '938 patent. In particular, the Examiner states that the present claims are not limited to any particular Helicobacter agent, while the claims of the '938 patent are limited to specific, enumerated agents.

In order for a genus/species relationship to exist, the genus must encompass all aspects of the species, and thus be broader than the species. This is not the case with the cited claims. The methods of the claims of the present application, for example, require the use of particular cationic lipids, saponins, or glycolipopeptides. The methods of the cited claims of the '938

patent, in contrast, do not require the use of such an agent. Thus, the claims of the present application are not genus claims, relative to the cited claims of the '938 patent. Applicants thus respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 39 was rejected under § 112, second paragraph for indefiniteness. The Examiner states that the number of compounds administered to a patient according to the method of this claim is only one, because the term "compound" is singular in line 3 of the claim. In addition, the Examiner notes that the term "composition" lacks antecedent basis in the claim, because the immunogenic agent and the compound are not specified as being part of the same composition.

Claim 39 has been amended to address this rejection. In particular, the claim has been amended to remove the term "composition," for which the claim lacks antecedent basis. It is intended that the claim covers the administration of an immunogenic agent derived from Helicobacter and a cationic lipid or salt thereof (the currently examined species), as is noted in the claim. The language of the claim is open, as the claim specifies that the method "comprises" administration of these agents. This means that it is possible that other agents are also administered. However, if only the minimum agents specified in the claim as now examined, a single immunogenic agent from Helicobacter and a single cationic lipid, are administered, the claim requires that the cationic lipid not be in the form of a liposome. Applicants submit that claim 39 now meets the requirements of § 112, second paragraph, and thus respectfully request that this rejection be withdrawn.

Claims 46-48 were rejected under § 112, second paragraph as being indefinite in stating that the T helper 1-type immune response is measured in mice, while claim 39, from which

claims 46-48 depend, specifies that the administration is to a patient. The Examiner further questions when after administration the immune response is evaluated, on the basis that it is likely that the ratio will change over time. Further, the Examiner states that the preambles of claims 46-48 specify that the claimed methods are for inducing a T helper 1-type response, while the remaining portions of these claims specify that a T helper 2-type response is induced at a level that is similar to, or substantially greater than, the level of the T helper 1-type response. This rejection is respectfully traversed.

Applicants first note that claim 46, from which claims 47 and 48 depend, has been amended to specify that the ratios recited in these claims are obtained when the method specified in claim 39 is carried out in a mouse. Thus, these claims further characterize the method of claim 39, carried out in a patient, by indicating ratios of antibodies that would be obtained if a corresponding method were to be carried out in a mouse.

Applicants further note that it is well known in the art that, in general, antibody responses reach a plateau 10-15 days after the last immunization step, and that levels generally remain constant for at least several weeks thereafter. Thus, those of skill in the art would know that, in order to obtain a ratio reflecting steady levels, it would be best to obtain measurements after about 10-15 days. Because the levels remain constant for several weeks thereafter, the precise time point after the 10-15 day period is not critical.

Applicants finally note that each of claims 46-48 requires the induction of a T helper 1-type immune response, and the details of these claims relating to the levels of T helper 2-type immune responses induced do not negate this fact. Rather, when the global immune response comprises a significant Th1 response, it is still within the present claims, even if this latter response is accompanied by a Th2 response that may be significant as well. In this case, the

global immune response is designated as a balanced Th1/Th2 response. In view of the above, applicants request that the rejections under § 112, second paragraph be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Claims 39, 44, and 49-57 were rejected under § 102(e) as being anticipated by U.S. Patent No. 6,126,938. This rejection is respectfully traversed.

The Examiner states that the '938 patent describes a method of inducing a T helper 1-type immune response to Helicobacter by administration of a Helicobacter-derived agent and a compound such as DC-chol. The Examiner refers to column 9, lines 45 and 46 of the '938 patent as teaching the use of DC-chol in these methods. Applicants note that claim 39, as amended herein, specifies that if the only agents being administered according the method of this claim are an immunogenic agent derived from Helicobacter and a cationic lipid, then the cationic lipid is not in the form of a liposome. At column 9, lines 45 and 46 of the '938 patent (the section referred to by the Examiner), the results of an experiment are described that employed the apoenzyme of *H. pylori* urease and DC-chol liposomes. Thus, the '938 patent does not anticipate the present claims, as the '938 methods that employ a cationic lipid, such as DC-chol, to induce a T helper 1-type immune response to an immunogenic agent from Helicobacter, have this agent in the form of a liposome, which is specifically excluded from the present claims. This rejection should therefore be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 39 and 43 were rejected under § 103(a) for obviousness over U.S. Patent No. 6,126,938, in view of U.S. Patent No. 5,283,185. The Examiner states that the '938 patent

teaches the administration of a nucleic acid molecule or antigen using DC-chol, but not DC-chol that is in the form of a dispersion, as is specified in claim 43. The Examiner cites the '185 patent as teaching formulation of DC-chol into a dispersion for the introduction of nucleic acid molecules into cells, and states that it would have been obvious to put the DC-chol of the '938 patent into a dispersion, as specified in the '185 patent, because the '185 patent shows that such dispersions facilitate the transfer of DNA into cells. This rejection is respectfully traversed.

As is noted above, DC-chol used in the '938 patent is in the form of a liposome, which is excluded from the present claims when the method involves the administration of an immunogenic agent from Helicobacter and a cationic lipid, in the absence of any other Th-1 inducing agents. Thus, the '938 patent does not provide any motivation to use cationic lipids in a non-liposome form. Motivation to use cationic lipids in this form, in conjunction with the administration of an *H. pylori* immunogenic agent, is also not provided by the '185 patent. This patent describes the use of cationic lipids, such as DC-chol, to facilitate the transfer of DNA into cells, which the '185 patent defines as transfection (column 1, lines 9 and 10). The only examples provided in the '185 patent demonstrate the introduction of DNA into tissue culture cells (see, e.g., Example XXI (column 12) and Example XXV (column 13)). Nowhere in the '185 patent is even the possibility of introducing DNA into cells *in vivo*, as would be done in an immunization method such as those now claimed, even mentioned. Moreover, the '185 patent specifies that the DNA/lipid mixtures are "incubated" with cells, not that they are administered to patients. Thus, because it is clear from reading the '185 patent that the methods described therein were intended solely for use *in vitro*, the '185 patent provides no motivation to modify the form of the cationic lipid of the '938 patent. Applicants thus respectfully request that this rejection be withdrawn.

Claims 39 and 43 were also rejected for obviousness over the '938 patent, in view of U.S. Patent No. 4,855,283, which describes a compound that can be used in the form of a suspension to induce an immune response to co-administered agents, such as bacterial antigens. The Examiner states that it would have been obvious to modify the form of the compound used in the method of the '938 patent to be in a dispersion, because the '283 patent shows that a compound in such a form is effective in stimulating a Th-1 immune response, as well as in enhancing a Th-2 immune response. This rejection is respectfully traversed.

The '283 patent does not provide any information as to what type of T-helper immune responses are induced using the adjuvants that the patent describes, and thus provides no basis for believing that any adjuvant, not to mention those of the present claims, could be used to induce an effective immune response against Helicobacter, including a Th-1 response. Indeed, while the '283 patent specifically states that the adjuvants described in the patent increase immunological reactivity by increasing the state of activity of macrophages (column 15, lines 23-50), the patent does not even mention T-helper 1-type cell-mediated immune responses at all. In addition, the glycolipopeptides of the '283 patent bear very little structural similarity to the cationic lipids now being examined in claims 39 and 43. These compounds have very different properties, which would certainly impact the manner in which they interact with one another, the molecules that they are used to deliver, the environments in which the delivery is to take place, and the cells to which they are delivering. Because of these differences, there would have been no expectation that merely the form in which a compound is administered would have the same effect on a completely different type of compound. Applicants thus request that this rejection be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: October 1, 2002

Susan M. Michaud

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045
50019.006001 reply to first office action.doc

21559
PATENT TRADEMARK OFFICE

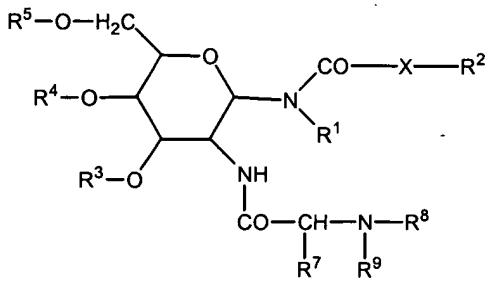
Version of Amended Claim with Markings to Show Changes Made

39. (Amended) A method of inducing a T helper 1-type immune response against Helicobacter in a patient, said method comprising administering to the patient an immunogenic agent derived from Helicobacter and a compound that promotes induction of a T helper 1-type immune response against Helicobacter, said compound being selected from the group consisting of:

(i) a saponin purified from an extract of *Quillaja saponaria*;

(ii) a cationic lipid or a salt thereof, wherein said lipid is a weak inhibitor of protein kinase C and has a structure that comprises a lipophilic group derived from cholesterol, a bonding group selected from carboxyamides and carbamoyls, a spacer arm consisting of a branched or unbranched linear alkyl chain of 1 to 20 carbon atoms, and a cationic amine group selected from primary, secondary, tertiary, and quaternary amines, wherein [and] said lipid is not provided in the form of a liposome when administered in the absence of any additional compounds that promotes induction of a T helper 1-type immune response against Helicobacter [when the composition does not comprise a saponin or a glycolipopeptide of formula (I)]; and

(iii) a glycolipopeptide of formula (I):



in which

R^1 represents an alkyl group that is saturated or unsaturated once or several times and comprises 1 to 50 carbon atoms;

X represents $-CH_2-$, -O-, or -NH-;

R^2 represents a hydrogen atom or an alkyl group that is saturated or unsaturated once or several times and comprises 1 to 50 carbon atoms;

R^3, R^4, and R^5 each represent, independently of each other, a hydrogen atom or an acyl-CO-R^6 group, in which R^6 represents an alkyl group comprising 1 to 10 carbon atoms;

R^7 represents a hydrogen atom or a C_1-C_7 alkyl, hydroxymethyl, 1-hydroxyethyl, mercaptomethyl, 2-(methylthio)ethyl, 3-aminopropyl, 3-ureidopropyl, 3-guanidylpropyl, 4-aminobutyl, carboxymethyl, carbamoylmethyl, 2-carboxyethyl, 2-carbamoylethyl, benzyl, 4-hydroxybenzyl, 3-indolylmethyl, or 4-imidazolylmethyl group;

R^8 represents a hydrogen atom or a methyl group; and

R^9 represents a hydrogen atom or an acetyl, benzoyl, trichloroacetyl, trifluoroacetyl, methoxycarbonyl, t-butyloxycarbonyl, or benzyloxycarbonyl group.

46. (Amended) The method of claim 39, wherein the T helper 1-type immune response is [measured in mice and is] characterized by a ratio of ELISA IgG2a:IgG1 titres that is greater than or equal to 1:20, when said method is carried out in a mouse, the IgG2a and IgG1 being immunoglobulins induced against Helicobacter.

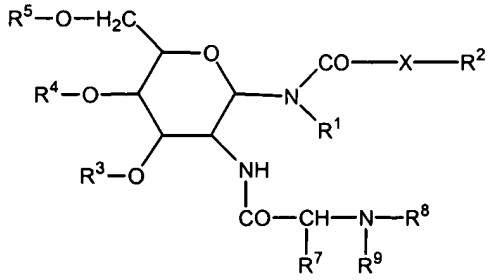
Pending Claims After Entry of Amendment

39. (Amended) A method of inducing a T helper 1-type immune response against Helicobacter in a patient, said method comprising administering to the patient an immunogenic agent derived from Helicobacter and a compound that promotes induction of a T helper 1-type immune response against Helicobacter, said compound being selected from the group consisting of:

(i) a saponin purified from an extract of *Quillaja saponaria*;

(ii) a cationic lipid or a salt thereof, wherein said lipid is a weak inhibitor of protein kinase C and has a structure that comprises a lipophilic group derived from cholesterol, a bonding group selected from carboxyamides and carbamoyls, a spacer arm consisting of a branched or unbranched linear alkyl chain of 1 to 20 carbon atoms, and a cationic amine group selected from primary, secondary, tertiary, and quaternary amines, wherein said lipid is not provided in the form of a liposome when administered in the absence of any additional compounds that promotes induction of a T helper 1-type immune response against Helicobacter; and

(iii) a glycolipopeptide of formula (I):



in which

R^1 represents an alkyl group that is saturated or unsaturated once or several times and comprises 1 to 50 carbon atoms;

X represents $-CH_2-$, -O-, or -NH-;

R^2 represents a hydrogen atom or an alkyl group that is saturated or unsaturated once or several times and comprises 1 to 50 carbon atoms;

R^3, R^4, and R^5 each represent, independently of each other, a hydrogen atom or an acyl-CO-R^6 group, in which R^6 represents an alkyl group comprising 1 to 10 carbon atoms;

R^7 represents a hydrogen atom or a C_1-C_7 alkyl, hydroxymethyl, 1-hydroxyethyl, mercaptomethyl, 2-(methylthio)ethyl, 3-aminopropyl, 3-ureidopropyl, 3-guanidylpropyl, 4-aminobutyl, carboxymethyl, carbamoylmethyl, 2-carboxyethyl, 2-carbamoylethyl, benzyl, 4-hydroxybenzyl, 3-indolylmethyl, or 4-imidazolylmethyl group;

R^8 represents a hydrogen atom or a methyl group; and

R^9 represents a hydrogen atom or an acetyl, benzoyl, trichloroacetyl, trifluoroacetyl, methoxycarbonyl, t-butyloxycarbonyl, or benzyloxycarbonyl group.

43. The method of claim 39, wherein the compound is a cationic lipid made in the form of a dispersion.

44. The method of claim 39, wherein the compound is the cationic lipid 3-beta-[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-chol) or a salt thereof.
49. The method of claim 39, wherein the immunogenic agent derived from Helićobacter is selected from the group consisting of a preparation of inactivated Helicobacter bacteria, a Helicobacter cell lysate, and a peptide or a polypeptide from Helicobacter in purified form.

46. (Amended) The method of claim 39, wherein the T helper 1-type immune response is characterized by a ratio of ELISA IgG2a:IgG1 titres that is greater than or equal to 1:20, when

said method is carried out in a mouse, the IgG2a and IgG1 being immunoglobulins induced against Helicobacter.

47. The method of claim 46, wherein the T helper 1-type immune response is characterized by a ratio of ELISA IgG2a:IgG1 titres that is greater than or equal to 1:10.

48. The method of claim 47, wherein the T helper 1-type immune response is characterized by a ratio of ELISA IgG2a:IgG1 titres that is greater than or equal to 1:2.

50. The method of claim 49, wherein the immunogenic agent derived from Helicobacter comprises the UreB or UreA subunit of Helicobacter urease.

51. The method of claim 39, wherein the immunogenic agent derived from Helicobacter is derived from *Helicobacter pylori*.

52. The method of claim 39, wherein the immunogenic agent and the compound are administered to the patient by a systemic route.

53. The method of claim 52, wherein the systemic route is the strict systemic route.

54. The method of claim 52, wherein the immunogenic agent and the compound are administered to the patient by a systemic route in a region of the patient that is situated under its diaphragm.

55. The method of claim 52, wherein the immunogenic agent and the compound are administered to the patient by a systemic route in the dorsolumbar region of the patient.

56. The method of claim 52, wherein the systemic route is selected from the group consisting of the subcutaneous route, the intramuscular route, and the intradermal route.

57. The method of claim 39, wherein the immunogenic agent and the compound are administered to the patient twice or three times by a systemic route during the same treatment.